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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PD/4-32803A	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/EP2004/003512	International filing date *(day/month/year)* 02.04.2004	Priority date *(day/month/year)* 04.04.2003
International Patent Classification (IPC) or national classification and IPC A61K31/593, A61K31/453, A61P17/00, A61P1/00		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 1 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 07.10.2004	Date of completion of this report 08.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Tardi, C Telephone No. +49 89 2399-8180

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003512

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-10 as originally filed

   Claims, Numbers

   1-5 received on 11.09.2004 with letter of 08.09.2004

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3

because:

☒ the said international application, or the said claims Nos. 3 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1,2,4,5
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 3 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:
   D1: WO 98/18468 A (AMERICAN HOME PROD) 7 May 1998
   D2: WO 02/094247 A (BIOXELL S P A ; ADORINI LUCIANO (IT); GREGORI SILVIA (IT); SMIROLDO SI) 28 November 2002
   D3: WO 02/064589 A (KOSAN BIOSCIENCES INC) 22 August 2002
   D4: WO 99/16745 A (WIESINGER HERBERT ; KIRSCH GERALD (DE); LANGER GERNOT (DE); SCHERING A) 8 April 1999

   Unless indicated otherwise, the relevant passages are those mentioned in the search report.

   D1 discloses the combination rapamycin + calcitriol for the treatment of psoriasis, dermatitis, eczema, Crohn's disease and inflammatory bowel disease.
   D2 discloses the combination of a vitamin D derivative + rapamycin or tacrolimus for the treatment of diabetes.
   D3 discloses that laulimalides (macrolide compounds) can be used in combination with vitamin D derivatives for the treatment of psoriasis and dermatitis.
   D4 discloses the combination of vitamin D derivatives with FK506 or rapamycin.

2) Novelty (Art. 33(2) PCT)
2.1 The combination of pimecrolimus with a calciferol, and its use for the treatment of skin diseases and/or of inflammatory bowel disease has not been described in the prior art (see D1-D4).
Therefore the subject-matter of claims 1-5 is new.

3) Inventive step (Art. 33(3) PCT)
Macrolides and Vitamin D derivatives have several therapeutical applications in common and the possibility to use them in combination has been described several times in the prior art (see D1-D4).
D1 e.g. discloses the combination rapamycin + calcitriol for the treatment of psoriasis, dermatitis, eczema, Crohn's disease and inflammatory bowel disease.

In the absence of any unexpected effect, pimecrolimus and calcipotriol or tacalcitol thus appear to be mere alternatives that the skilled man could have chosen without the involvement of any inventive step.
Therefore the subject-matter of claims 1-5 does not fulfill the requirements of Art. 33(3) PCT.

4) For the assessment of the present claim 3 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims:

amended 8-September-2004

1. A pharmaceutical composition comprising pimecrolimus in combination or association with a calciferol together with at least one pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1 wherein the calciferol is calcipotriol or tacalcitol.

3. A method of treatment of a dermatological disease such as atopic dermatitis, acne or psoriasis, or of inflammatory bowel disease (IBD), in a subject suffering from or at risk for such condition, comprising co-administering a synergistically effective amount of a composition according to claim 1.

4. A process for the preparation of a composition of claim 1 comprising mixing pimecrolimus and a calciferol in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising pimecrolimus and a calciferol in separate unit dosage forms together with instructions for use.